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<b>(54) Title:</b> THE USE OF 5-AMINOSALICYLIC ACID IN THE TREATMENT OF IRRITABLE BOWEL SYNDROME - DIARRHEAL PHASE OR TYPE (IBS-D)  <b>(57) Abstract</b>  Treatment for a human or other mammal afflicted with IBS-D, comprising the topical delivery to the intestinal tract of said human or other mammal, preferably the large intestine, of a safe and effective amount of a pharmaceutical composition consisting essentially of the 5-ASA active ingredient and pharmaceutically-acceptable excipients. Said topical delivery is preferably accomplished by the oral administration to said human or other mammal of a delayed-release composition consisting essentially of said 5-ASA active ingredient and a pharmaceutically-acceptable excipient.		

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THE USE OF 5-AMINOSALICYLIC ACID IN THE TREATMENT OF  
IRRITABLE BOWEL SYNDROME - DIARRHEAL PHASE OR TYPE (IBS-D)

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BACKGROUND OF THE INVENTION

The present invention relates to the novel method of treating a human or other mammal afflicted with Irritable Bowel Syndrome - Diarrheal Phase or Type (hereinafter referred to as IBS-D) comprising the topical delivery to the intestinal tract of said human or other mammal of a safe and effective amount of a pharmaceutical composition consisting essentially of the active ingredient 5-aminosalicylic acid (hereinafter referred to as "5-ASA"), and pharmaceutically-acceptable excipients. Said topical delivery is most preferably accomplished by the oral administration to said human or other mammal of a delayed-release composition consisting essentially of said 5-ASA active ingredient and a pharmaceutically-acceptable excipient.

Irritable bowel syndrome (hereinafter referred to as "IBS") is a poorly understood disorder for which there is presently no adequate treatment. IBS is usually the diagnosis given when an individual suffers from certain characteristic symptoms affecting the gastrointestinal tract and after the existence of other disorders have been eliminated. Accordingly, IBS sufferers exhibit altered bowel habits (characterized either by alternating diarrhea and constipation, solely constipation, or solely diarrhea), as well as abdominal pain and/or cramping, and various other symptoms including flatulence and abdominal distension, bloating, and rumbling. There is no detectable radiological or histological evidence of organic pathology, i.e. the presence of an infectious agent or observable inflammation or other pathology in the intestinal tract. IBS has been called functional bowel

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disorder, mucomembraneous colitis, nervous diarrhea, colonic neurosis, colonic dyspepsia, colonic dysfunction, spastic colon, mucous colitis, irritable colon syndrome, unhappy colon, dissynergia of the colon, and disordered gastrocolonic reflex.

5 It is estimated that about 10% of the adult population suffers from IBS and that this disorder accounts for from about 40% to about 70% of office visits to gastroenterologists. It has also been suggested that IBS is one of the leading causes of absenteeism from work due to illness.

10 As stated hereinabove, those suffering from IBS may experience diarrhea only, alternating diarrhea and constipation, or constipation only; accordingly, there has been a great deal of effort to categorize IBS patients based upon these symptoms. See Einar Krag, "Irritable Bowel Syndrome: Current Concepts and  
15 Future Trends," Scand. J. Gastroenterol., Vol. 20 (Suppl. 109), pp. 107-15, 1985; and Whitehead et al., "Irritable Bowel Syndrome - Physiological and Psychological Differences Between Diarrhea-Predominant and Constipation-Predominant Patients", Dig. Dis. Sci., Vol. 25, No. 6, pp. 404-13, June 1980 (hereinafter  
20 referred to as "Whitehead et al."). It has been estimated that about 50% of IBS sufferers experience IBS-Diarrheal phase or type (hereinafter referred to as IBS-D) and that 50% of IBS sufferers experience constipation only. Of the population which suffers from IBS-D, one-fifth experience only diarrhea (IBS-diarrheal  
25 type), and the remaining four-fifths experience alternating diarrhea and constipation (IBS-diarrheal phase).

The cause of IBS has been extremely difficult to determine, and there has been little success in differentiating possible causes with regard to symptomatic characterizations. It has been  
30 reported that IBS stems from the ingestion of certain foodstuffs (often wheat gluten or lactose); other theories as to the cause of IBS have implicated disorders of gut motility, while many gastroenterologists, however, have attributed IBS to psychological factors. See generally, V. Alun Jones, et al.,  
35 "Food Intolerance: A Major Factor in the Pathogenesis of Irritable Bowel Syndrome", The Lancet, Vol. 2, No. 8308,

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pp. 1115-17, November 20, 1982 (hereinafter referred to as "Jones et al."); Kumar et al., "The Irritable Bowel Syndrome: A Paroxysmal Motor Disorder", The Lancet, Vol. 2, No. 8462, pp. 973-77, November 1985 (hereinafter referred to as "Kumar et al."); Drossman et al., "Psychosocial Factors in the Irritable Bowel Syndrome," Gastroenterology, Vol. 95, (3), pp. 701-8, Sept. 1988; and Drossman et al., "The Irritable Bowel Syndrome," Gastroenterology, Vol. 73, p. 811-22, Oct. 1977.

In addition to confusion as to the cause of IBS-D, there is debate as to the precise site of the disorder in the intestinal tract; there is confusion as to whether the problematic region is the small intestine, the colon, or both, and whether the problematic site varies amongst individuals and/or depending on the symptoms. See, e.g. Kumar et al., op. cit., and Cann et al., "Irritable Bowel Syndrome: Relationship of Disorders in the Transit of a Single Meal to Symptom Patterns", Gut, Vol. 24, No. 5, pp. 405-11, May 1983.

Much of the early work on disorders of the gastrointestinal tract has involved ulcerative colitis and Crohn's disease, which are two of the most common Inflammatory Bowel Diseases (hereinafter referred to as "IBD"). In fact, patients with IBS-D present with symptoms which are markedly similar to those experienced with IBD, particularly ulcerative colitis and Crohn's disease and, therefore, the existence of IBD is generally investigated and ruled out before the diagnosis of IBS-D is given.

It has been reported that the administration of 5-ASA is effective in the treatment of ulcerative colitis and Crohn's disease. See U.S. Patent 4,496,552 to Halskov, issued January 29, 1985, and assigned to Farmaceutisk Laboratorium Ferring, hereby incorporated by reference herein.

It has further been stated that various gastrointestinal disorders including, in addition to IBS, Crohn's disease (regional ileitis), ulcerative colitis (proctitis, distal proctocolitis), atrophic gastritis, stump proctitis, coeliac disease, regional ileitis, peptic ulceration, and

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gastrointestinal allergy respond to treatment by a pharmaceutical composition comprising a compound having sodium cromoglycate-like activity as the active ingredient, in combination with sulfasalazine or an ASA. See U.K. Patent Publication  
5 GB 2,021,409 of Worsley, published December 5, 1979, assigned to Fisons Ltd., hereby incorporated by reference herein, along with its U.S. equivalent, U.S. Patent 4,211,777 to Chambers, issued July 8, 1980, assigned to Fisons Ltd., hereby incorporated by reference herein.

10       Ulcerative colitis is a chronic inflammatory disease of the colon of unknown etiology. The disease causes inflammation of the mucosa of the colon, with extension to the submucosa in severe cases. Typically, the colon, as well as the rectum, is involved; it is less common for the ileum (the most distal  
15 portion of the small intestine) to be involved. The ulcer formation and its extent may vary amongst individuals and amongst different regions of the intestinal tract of the same individual, and is often detectable via sigmoidoscopy or colonoscopy. Crohn's disease, also known as regional enteritis or colitis  
20 granulomatosa, is often characterized as being related to ulcerative colitis, since they are both inflammatory diseases of the intestine. Crohn's disease is most frequently located in the small intestine, especially in the ileum, but also may affect the jejunum (the middle part of the small intestine, just distal to  
25 the duodenum and proximal to the ileum) and any part of the colon, including the rectum. When the colon is involved, the differentiation of Crohn's disease from ulcerative colitis is considerably difficult. Generally, the inflammatory reaction of Crohn's disease differs from that of ulcerative colitis by  
30 progressing to layers deeper than the mucosa and affecting the epithelium to a lesser degree. A thorough review of both diseases is given by J. B. Kirsner, M.D., Ph.D., in an article entitled "Observation on the Medical Treatment of Inflammatory Bowel Disease," found in JAMA, Feb. 8, 1980, Vol. 243, No. 6, pp.  
35 557-564.

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IBD is distinguished from IBS by the presence of the inflammation of the mucosa and submucosa layers of the intestine, which is detectable usually by visual inspection (sigmoidoscopy or colonoscopy), but also by radiological or histological examination. As stated hereinabove, IBS is characterized by the lack of any detectable radiological or histological evidence of organic pathology, such as observable inflammation of layers deeper than the epithelium. For further discussions comparing IBD with IBS, see, e.g., Thompson, "Gastrointestinal Symptoms in the Irritable Bowel Compared with Peptic Ulcer and Inflammatory Bowel Disease," Gut, Vol. 25, No. 10, pp. 1089-92, Oct. 1984; Whitehead et al., op cit.; Isgar et al., "Symptoms of Irritable Bowel Syndrome in Ulcerative Colitis in Remission," Gut, Vol. 24, pp. 190-2, 1983; and Ahnfelt-Ronne et al., "Clinical Evidence Supporting the Radical Scavenger Mechanism of 5-ASA," Gastroenterology, Vol. 98, No. 5, pp. 1162-69, May 1990.

For many years, it has been hypothesized that prostaglandins were somehow implicated in various gastrointestinal disorders, including IBS-D and IBD. As the outline of current research set forth hereinbelow illustrates, there is considerable debate as to the role of prostaglandins in the etiology of both IBS-D and IBD, and whether prostaglandins actually cause, or are merely the result of, inflammation of the intestinal tract. In addition, as the discussion hereinabove shows, IBS-D is an entirely different entity than IBD, and conclusions drawn regarding one cannot be likewise applied to the other.

In a symposium on prostaglandins, Donald E. Wilson, M.D. and Hulya Kaymakcelan, M.D. reviewed the role of prostaglandins in various gastrointestinal disorders, including IBS. See Wilson, et al., "Prostaglandins: Gastrointestinal Effects and Peptic Ulcer Disease", Med. Clin. North. Am., Vol. 65, No. 4, pp. 773-87, July 1981, hereinafter referred to as "Prostaglandins". It was reported therein that the possible role of prostaglandins in specific and nonspecific inflammatory disorders has been suggested by several studies indicating that the condition of patients with a variety of intestinal disorders

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(including, in addition to IBS, radiation enteritis, ulcerative colitis, and food intolerance) improved when inhibitors of prostaglandin synthesis, such as aspirin or indomethacin, were administered. See Prostaglandins, pp. 781-2. Also reported  
5 therein, however, was the fact that information linking prostaglandins to said disorders is in a state of flux and the role of prostaglandins in IBS-D is uncertain. The confusion is exacerbated by the fact that "prostaglandins are a normal by-product of the inflammatory response and the finding of  
10 elevated prostaglandin levels on inflammation does not necessarily indicate a pathogenetic role for prostaglandins." See Prostaglandins at 782.

It was reported that indomethacin blockade appeared to exhibit important therapeutic implications with IBS-D. See  
15 J. Rask-Madsen et al., "Indomethacin-Responsive Diarrhea in Irritable Bowel Syndrome", Gut, Vol. 19, p. 448, 1978. It was reported by Jones et al., op. cit., p.1117 that there were significant elevations of PGE<sub>2</sub> levels in their patients after food challenge and a significant relationship between PGE<sub>2</sub> and  
20 wet fecal weight. It was suggested therein that these results indicate that prostaglandins may be associated with the etiology of IBS-D. At the same time, Jones et al. also reported that IBS patients who were experiencing pain rather than diarrhea did not show pronounced increase in prostaglandin production and further  
25 hypothesized that other factors may be important in the etiology of IBS-D. There are also reports that in a few cases the oral administration of various Non-Steroidal Anti-Inflammatory Drugs (hereinafter "NSAIDs") cause exacerbations of colitis. See Clements et al., "Colitis Associated with Ibuprofen", British  
30 Medical Journal, Vol. 301, No. 6758, p. 987, Oct. 22, 1990, and references cited therein. For an additional discussion of the treatment of IBS with prostaglandin inhibitors, see, e.g. Lessof et al., "Prostaglandins in the Pathogenesis of Food Intolerance", Annals of Allergy, Vol. 51, pp. 249-50, August 1983.

35 Hawkey and Truelove extensively discussed the role of prostaglandins in ulcerative colitis. See Hawkey, C.J., and



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Truelove, S. C., "Inhibition of Prostaglandin Synthetase in Human Rectal Mucosa", Gut, 1983, 24, pp. 213-7 (hereinafter "Hawkey et al.") It was reported therein that there are some indications that prostaglandin synthesis is associated with an excessive inflammatory reaction and that inhibition of this synthesis is therefore desirable. However, it has also been shown that indomethacin and flurbiprofen (which are more potent than 5-ASA as inhibitors of prostaglandin synthesis by human rectal mucosa) do not appear to be effective agents in the treatment of ulcerative colitis. In fact, extremely deleterious effects have been reported with the use of flurbiprofen to treat ulcerative colitis. Id at 216. These findings suggest that the inhibition of prostaglandin synthesis alone may not be the precise mechanism by which 5-ASA works to alleviate ulcerative colitis.

Such results with potent prostaglandin inhibitors have led to the alternative view that prostaglandins may be cyto-protective in ulcerative colitis. Data have been generated which shows that, in some circumstances, 5-ASA, although usually characterized in a general fashion as a prostaglandin inhibitor, might lead to enhanced rather than reduced levels of mucosal prostaglandins. Id.

Hawkey et al. also proposed a third possible theory as to the mode of action of 5-ASA in ulcerative colitis. Weak inhibitors of prostaglandin synthetase (such as 5-ASA) have been shown to decrease synthesis of leukotrienes and hydroxyeicosatetraenoic acids by inhibiting the lipoxygenase pathways which may lead to their production; leukotrienes and hydroxyeicosatetraenoic acids are non-prostaglandin hydroxy end products of arachidonic acid metabolism associated with an ability to reduce the accumulation of white cells at sites of inflammation. By contrast, potent prostaglandin synthetase inhibitors (such as indomethacin and flurbiprofen) have little effect on white cell accumulation and can, therefore, divert arachidonic acid metabolism along lipoxygenase pathways which have been shown to exist in human colonic mucosa. Id. For further discussions of the possible role of prostaglandins in

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Inflammatory Bowel Disease, see e.g. Ligumsky et al., "Enhanced Thromboxane A<sub>2</sub> and Prostacyclin Production by Cultured Rectal Mucosa in Ulcerative Colitis and Its Inhibition by Steroids and Sulfasalazine," Gastroenterology, Vol. 8, No. 3, pp. 144-9, 5 September 1981; Pacheco, "Inflammatory Bowel Disease: The In Vitro Effect of Sulphasalazine and Other Agents on Prostaglandin Synthesis by Human Rectal Mucosa," Braz. J. Med. Biol. Res., Vol. 20, No. 3, pp. 221-230, 1987; Campieri et al., "Salicylate Other Than 5-Amino Salicylic Acid Ineffective in Ulcerative Colitis," 10 (letter), The Lancet, p. 993, Nov. 4, 1978; and Donowitz, "Arachidonic Acid Metabolites and Their Role in Inflammatory Bowel Disease: An Update Requiring Addition of a Pathway," Gastroenterology, Vol. 88, No. 2, pp. 580-7, 1985.

The outline of current research set forth hereinabove serves 15 to illustrate the state of immense confusion which exists regarding the role of prostaglandins in both ulcerative colitis and IBS-D. The discussion hereinabove shows the confusion is further complicated by the fact that there is disagreement as to whether 5-ASA inhibits or enhances prostaglandin synthesis and by 20 the fact that there is considerable debate as to whether prostaglandins aggravate or alleviate both, or either, ulcerative colitis and IBS-D. Furthermore, the relevance of the effect of 5-ASA in inhibiting production of leukotrienes and hydroxyeicosatetraenoic acids to its therapeutic effects in IBS-D and IBD is 25 yet to be determined.

In addition, as stated hereinabove, it is a fact that prostaglandins are a normal by-product of an inflammatory response [such as that which would accompany both the topical (epithelial cells most near the intestinal lumen) irritation 30 accompanying diarrhea in IBS-D as well as the deeper irritation indicative of mucosal and/or submucosal inflammation of IBD]; accordingly, elevated prostaglandin levels in disorders characterized by inflammation does not necessarily mean prostaglandins caused the inflammation. Finally, the confusion 35 is even further amplified by the facts that the manifestations of ulcerative colitis, and other IBDs, as compared to those of

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IBS-D, are markedly distinct and that the etiology of both IBD and IBS-D are unknown; accordingly, data generated and conclusions drawn regarding ulcerative colitis, and other forms of IBD, cannot, in the current state of knowledge, be applied to  
5 IBS-D.

Probably largely due to the fact that the etiology of IBS-D is unknown, there is no satisfactory treatment for IBS-D at the present time. Conventional treatment has included various types of therapies including antispasmodic agents (octilonium bromide,  
10 mebeverine, trimebutine, dicyclomine, and prifinium bromide); anticholinergic agents (atropine, belladonna, 1-hyoscyamine, propantheline bromide, and dicyclomine hydrochloride); anticholinergic/barbiturate combinations (tricyclamol and/or phenobarbital; dicyclomine and/or phenobarbital); antidepressants  
15 (desipramine, trimipramine, amitriptyline); bulking agents (wheat bran, psyllium (ispaghula)); dopamine antagonists (domperidone); carminatives (peppermint oil); opioids (loperamide); tranquilizers or tranquilizer combinations (mepiprazol, benzodiazepine, trimipramine, phenaglycodol, meprobamate, fluphenazine and  
20 nortriptylene, lorazepam and/or hyoscyne and/or ispaghula) and miscellaneous actives such as phenytoin (an anticonvulsant), timolol (a  $\beta$ -adrenergic receptor-blocker), and diltiazem (a calcium channel blocker). Said conventional therapies have been usually unsatisfactory and are often accompanied by serious and  
25 undesirable side effects; accordingly, many symptoms of IBS-D go untreated. See, e.g., Jones, et al., op. cit., pp. 1115-7; Klein, "Controlled Treatment Trials in the Irritable Bowel Syndrome: A Critique", *Gastroenterology*, Vol. 95, pp. 232-41, 1988; Waller et al., "Prognosis in Irritable Bowel Syndrome", *The Lancet*, Vol. ii, pp. 753-56, 1969; G. Misiewicz, "Gastrointestinal Manifestations of Stress and Psychopathic Personality", *Medicine*, Vol. 3, pp. 183-88, 1972.  
30

Applicants have found that a human or other mammal suffering from IBS-D can be successfully treated with the topical delivery  
35 of 5-ASA or its salts and esters, to the intestinal tract of said human or mammal, preferably the large intestine. The 5-ASA

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active ingredient has been shown to be effective alone, with no sodium cromoglycate-like agent, and to be generally well tolerated, with minimal to substantially no side effects. It is preferred to effect said topical delivery of the 5-ASA active ingredient by the oral administration of delayed-release tablets. Said delayed-release tablets are most preferably formulated in such a way that the 5-ASA active ingredient is substantially topically delivered to the large intestine via a release of the active ingredient at a pH which is generally present only in the large intestine.

Although the preferred method of treatment described herein is the topical delivery of the 5-ASA active ingredient to the large intestine, topical delivery of the active ingredient to the small intestine may be desirable alone, or in addition to, the topical delivery to the large intestine. Of course, the segment of the intestine to which the active ingredient will be topically delivered can be varied by employing various standard pharmaceutical dosage forms as delivery systems. When utilizing oral dosage forms, it is generally easier, and therefore more preferable, to vary coating methods, types, and/or thicknesses which are readily available to those skilled in the art.

#### SUMMARY OF THE INVENTION

The present invention embodies a novel method of treatment for a human or other mammal afflicted with IBS-D, which comprises the topical delivery to the intestinal tract of said human or other mammal of a safe and effective amount of a pharmaceutical composition consisting essentially of a 5-ASA active ingredient, and pharmaceutically-acceptable excipients. Said topical delivery is preferably to the large intestine of said human or other mammal and is most preferably accomplished by the oral administration to said human or other mammal of a delayed-release composition consisting essentially of said 5-ASA active ingredient and pharmaceutically-acceptable excipients.

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DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a novel method of treatment for a human or other mammal afflicted with IBS-D which comprises the topical delivery to the intestinal tract of said human or other mammal, preferably to the large intestine, of a safe and effective amount of a pharmaceutical composition consisting essentially of a 5-ASA active ingredient and pharmaceutically-acceptable excipients. Said topical delivery is most preferably achieved via the oral administration to said human or other mammal of a delayed-release composition consisting essentially of the 5-ASA active ingredient and pharmaceutically-acceptable excipients.

A. The 5-ASA Active Ingredient

The present invention is directed to a method of treatment for IBS-D utilizing the topical delivery to the intestinal tract of a human or other mammal, preferably to the large intestine, of a safe and effective amount of a pharmaceutical composition consisting essentially of a 5-ASA active ingredient and pharmaceutically-acceptable excipients.

The term "5-ASA active ingredient", as used herein, denotes 5-aminosalicylic acid, hereinafter referred to as "5-ASA" and, unless otherwise specified, encompasses the pure compound 5-aminosalicylic acid, as well as the pharmaceutically-acceptable salts or esters thereof, or any mixture thereof. 5-Aminosalicylic acid (5-ASA) is often referred to as "mesalamine" and "mesalazine" and is more properly referred to as 5-amino-2-hydroxybenzoic acid or 5-amino-2-hydroxybenzene-1-carboxylic acid.

Any pharmaceutically-acceptable, non-toxic salt of 5-ASA may be used as the 5-ASA active ingredient in the composition of the present invention. The salts of 5-ASA may be acid addition salts, in particular the hydrochloride, but any pharmaceutically-acceptable, non-toxic organic or inorganic acid salt may be used. In addition, salts formed with the carboxylic acid group may be used, including, but not limited to, alkali

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metal salts (K, Na) and alkaline earth metal salts (Ca, Mg), the Ca- and Na- salts being preferred.

Any pharmaceutically-acceptable, non-toxic ester of 5-ASA may be used as the 5-ASA active ingredient in the pharmaceutical composition described herein. Particularly suitable esters are those meta- (or 5-) aminosalicylic esters and a number of related esters disclosed in Great Britain Patent Specification 1,581,444 of Halpern et al., assigned to Mundipharma A.G. of Switzerland, published December 17, 1980, hereby incorporated herein by reference. A number of esters of ortho-, meta-, and para-salicylic acid are disclosed. Said esters are effective as ultraviolet ray screening compounds, thereby rendering themselves useful in preventing solar burning.

Other esters of 5-ASA which are suitable for use as the active ingredient in the invention disclosed herein are straight chain or branched chain C<sub>1</sub>-C<sub>18</sub> alkyl esters, including, but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, amyl, hexyl, heptyl, octyl, nonyl, decyl, lauryl, myristyl, cetyl, and stearyl; straight chain or branched C<sub>2</sub>-C<sub>18</sub> alkenyl esters, including, but not limited to, vinyl, alkyl, undecenyl, and linolenyl; C<sub>3</sub>-C<sub>8</sub> cycloalkyl esters, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl; aryl esters, including, but not limited to, phenyl, toluyl, xylyl, and naphthyl; alicyclic esters, including, but not limited to, menthyl; and aralkyl esters, including, but not limited to, benzyl, and phenethyl.

Generally speaking, the proper selection of the 5-ASA active ingredient depends on the selected type of formulation, the disease pattern, especially the site and type of the disease, and the desired release of the active ingredient. In addition, the physical and chemical characteristics of the active ingredient must be taken into account when selecting suitable pharmaceutically-acceptable excipients for use in the pharmaceutical composition containing the 5-ASA active ingredient.

In addition to the 5-ASA active ingredients, the pharmaceutical composition and methods of the present invention may

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also contain other non-5-ASA active agents exhibiting different and/or additional biological activity. For instance, those compounds conventionally used in the treatment of diseases or disorders of the intestinal tract are of particular interest. In addition to 5-ASA active ingredients, examples of other non-5-ASA active agents include non-steroidal anti-inflammatory drugs (i.e., NSAIDs), as described hereinbelow, preferably including, but not limited to, salicylates, indomethacin, flurbiprofen, diclofenac, naproxen, piroxicam, tebufenone and ibuprofen; steroids, including, but not limited to, hydrocortisone, prednisolone, prednisolone phosphate, prednisolone metasulpho-benzoate sodium, prednisolone sodium phosphate, beclomethasone diphosphonate, and beclomethasone valerate; compounds active in the relief of constipation and diarrhea; compounds active in the relief of spasm and in the improvement of motility, e.g. peppermint oil and other carminative essential oils; compounds for the removal of excessive bile acids, including, but not limited to cholestyramine; antibacterial or antiparasite compounds, including, but not limited to, erythromycin, chloroquine, iodochlorhydroxyquine, disodohydroxyquine, neomycin and tetracyclines. Non-5-ASA active agents do not include sodium cromoglycate.

Other non-5-ASA active agents suitable for use herein are 5-aminosalicylic acid NSAID conjugates described by Moller et al., "Novel 5-Aminosalicylic Acid NSAID Conjugates: Synthesis, Pharmacological and Toxicological Properties," Europ. J. Med. Chem., Vol. 24, No. 5, pp. 463-69, 1989, hereby incorporated by reference herein. The described conjugates are produced by coupling the NSAID carboxyl-group with the 5-amino-group of 5-ASA. The 5-ASA derivatives of the NSAIDs diclofenac, ibuprofen, indomethacin, naproxen, and salicylic acid are particularly described, but conjugates of 5-ASA active ingredients and other NSAIDs are suitable for use as a non-ASA active agent in the method of treatment of the invention herein.

The term "NSAIDs" as used herein is an abbreviation for the phrase "Non-Steroidal Anti-Inflammatory Drugs" and includes, but

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is not limited to, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrnone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchophen, clonixin, ditrazol, epirizole, fenoprofen, floctafenine, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen, and tolmetin, preferably flurbiprofen, ibuprofen, indomethacin, naproxen, piroxicam, salicylates, diclofenac, and tebufelone.

10       The effective oral dose depends on the extent of the disease and for adults it usually amounts to from about 1.0 g to about 6.0 g daily, preferably from about 2.0 g to about 5.0 g daily, most preferably from about 2.4 g to about 4.8 g daily. Generally, for oral administration, it is preferable to divide  
15       the total daily dosage into four equal parts, most preferably to be taken immediately before meals and at bedtime. For rectal administration, the daily dose is preferably from about 1.0g to about 4.0g. When rectal administration is in the form of a suppository, the most preferred daily dose is about 1.0g to about  
20       2.0g, and it is generally preferable to divide the total daily dosage into two parts, one to be administered during the day and the other at bedtime. When the rectal administration is in the form of an enema, the most preferred daily dose is about 4.0g and it is generally preferable to administer the entire daily dosage  
25       in the form of a retention-type enema at bedtime.

B. Site of Topical Delivery of the 5-ASA Active Ingredient

A human or other mammal suffering from IBS-D can be successfully treated by the topical delivery of the 5-ASA active ingredient to the intestinal tract of said human or other mammal, preferably the large intestine. In some instances, however, it may be desired to topically deliver the 5-ASA active ingredient to the entire intestinal tract, beginning with topical delivery to the small intestine and continuing with delivery to the large intestine; in other cases, delivery of the 5-ASA active  
30       ingredient to the small intestine only may be desired.  
35



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The term "large intestine" as used herein includes that part of the intestine just distal to the small intestine, beginning with the cecum, including the ascending colon, the transverse colon, the descending colon, the sigmoid colon, and the rectum.

5 The preferred method of treatment for IBS-D as defined herein comprises the topical delivery of the 5-ASA active ingredient to the large intestine. Said topical delivery is preferably achieved via a delayed-release oral dosage form prepared utilizing a pH-dependent coating which does not dissolve to

10 release said active ingredient at pH below 7.0, but does dissolve at pH of 7.0 or above. The said preferred method achieves the release of the active ingredient when the pH rises above 7.0, and this, for all practical purposes, results in release in the large intestine, generally beginning in the cecum. This method is

15 preferred because it is believed that, for most IBS-D sufferers for most of the time, the problematic region of the intestinal tract is in the large intestine.

In some individuals, and/or at different times in the same individual, the pH rises to 7.0 or above in the terminal ileum,

20 which by strict anatomical definition is part of the small intestine. However, the preferred method herein involves the topical delivery of the 5-ASA active ingredient effected by release at a pH of 7.0 or above, generally, for most individuals most of the time, in the large intestine.

25 The term "small intestine" as used herein means the duodenum, the jejunum, and the ileum, i.e., that portion of the intestinal tract just distal to the duodenal sphincter of the fundus of the stomach and proximal to the large intestine.

30 C. Pharmaceutical Compositions to Effect Topical Delivery of the 5-ASA Active Ingredient to the Intestinal Tract

As stated hereinabove, the present invention is directed to a method of treatment for IBS-D utilizing the topical delivery to the intestinal tract of a human or other mammal, preferably to the large intestine, of a safe and effective amount of a

35 pharmaceutical composition consisting essentially of a 5-ASA active ingredient and pharmaceutically-acceptable excipients.

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Although it is certainly more preferred to achieve topical delivery of the 5-ASA active ingredient via an oral dosage form (i.e., either via delayed-release formulations or sustained-release formulations), any dosing method of the pharmaceutical composition which achieves topical delivery of the 5-ASA active ingredient to the intestinal tract is suitable for use as the method of treatment for IBS-D described herein. Accordingly, oral dosage forms suitable for use herein may be delayed-release formulations or sustained-release formulations. Topical delivery of the 5-ASA may also be achieved via rectal administration including, but not limited to, enemas and suppositories. The active ingredient compositions can be formulated as tablets, capsules, suppositories or suspensions along with suitable pharmaceutical excipients which are well-known to those skilled in the art are described hereinbelow.

The term "pharmaceutical composition" means a combination consisting essentially of the 5-ASA active ingredient and pharmaceutically-acceptable excipients. The pharmaceutical composition may additionally contain certain non-5-ASA active agents which will be described in detail hereinbelow.

The phrase "safe and effective amount", as used herein, means an amount of a compound or composition high enough to significantly positively modify the symptoms and/or condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of active ingredient for use in the method of the invention herein will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient being employed, the particular pharmaceutically-acceptable excipients utilized, and like factors within the knowledge and expertise of the attending physician.

The term "pharmaceutically-acceptable excipients" as used herein includes any physiologically inert, pharmacologically

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inactive material known to one skilled in the art, which is compatible with the physical and chemical characteristics of the particular 5-ASA active ingredient selected for use. Pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, lubricants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes or pigments, and viscosity agents.

The term "oral dosage form" as used herein means any pharmaceutical composition intended to be administered to the gastrointestinal tract of an individual via the mouth of said individual, and for purposes of the present invention, the delivered form can be in the form of a tablet, suspension, or a capsule, coated or non-coated.

The term "delayed-release" as used herein refers to a topical delivery of an active ingredient which is effected by formulating the active ingredient in a pharmaceutical composition so that the release will be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no alteration in the delivery of the active ingredient. The preferred method for effecting the delayed-release of the active ingredient involves coating (or otherwise encapsulating) said active ingredient with a substance which is not absorbed, or otherwise broken down, by the intestine to release said active ingredient until a specific desired point in the intestinal tract is reached. The most preferred type of delayed-release formulation for use herein is achieved by coating the active ingredient with a substance which is pH-dependent, i.e., broken down at a pH which is generally present in the large intestine. However, if it is desired to effect the topical delivery via the oral administration of a pharmaceutical composition containing the 5-ASA-active ingredient to only the small intestine, or to the entire length of the intestinal tract beginning with the small intestine, then the selection of the coating material and/or the method of coating or otherwise combining the 5-ASA

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active ingredient with the selected coating material or other pharmaceutically-acceptable excipients may be varied or altered as is described herein or by any method known to one skilled in the art.

5       The term "sustained-release" as used herein means the type of release mechanism designed to effect the topical delivery of the active ingredient over an extended period of time, as contrasted to the delivery of a delayed-release type dose. The most preferred sustained-release type method for use herein  
10 involves the coating of granules of the 5-ASA active ingredient with a pH-independent coating and is described in U.S. Patent 4,496,552 to Halskov, incorporated by reference previously herein. Said sustained-release dosage form effects the topical delivery of the 5-ASA active ingredient to both the small  
15 intestine and the large intestine.

As stated hereinabove, the ultimate site of and/or the rate of topical delivery in the intestinal tract can be satisfactorily controlled by one skilled in the art, by manipulating any one or more of the following:

- 20       (a) the active ingredient proper;  
         (b) the type of the coating, and the concomitant desirable thickness and permeability (swelling properties) of said coating;  
         (c) the time-dependent conditions of the coating itself and/or within the coated tablet, particle, or granule;  
25       (d) the particle size of the granulated active ingredient;  
         and  
         (e) the pH-dependent conditions of the coating itself and/or within the coated tablet, particle, or granule.

30       In particular, the solubility, acidity, and susceptibility to hydrolysis of the different 5-ASA active ingredient, such as acid addition salts, salts formed with the carboxylic group, e.g., alkali metal salts, alkaline earth metal salts, etc., and esters, e.g., alkyl, alkenyl, aryl, aralkyl, may be used as guidelines for the proper choice. In addition, suitable  
35 pH-conditions might be established within the coated particles by

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adding a suitable buffer to the active ingredient in accordance with the desired release pattern.

Besides the above mentioned variations in order to obtain the desired release pattern, the excipients may also be varied, as long as they do not affect the activity of the particular 5-ASA active ingredient selected.

As stated hereinabove, pharmaceutically-acceptable excipients include, but are not limited to, polymers, resins, plasticizers, fillers, lubricants, solvents, cosolvents, surfactants, preservatives, sweetener agents, flavoring agents, buffer systems, pharmaceutical-grade dyes or pigments, and viscosity agents.

The preferred solvent is water.

Flavoring agents among those useful herein include those described in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, 1990, pp. 1288-1300, incorporated by reference herein. Dyes or pigments among those useful herein include those described in Handbook of Pharmaceutical Excipients, pp. 81-90, 1986 by the American Pharmaceutical Association & the Pharmaceutical Society of Great Britain, incorporated by reference herein.

Preferred co-solvents include, but are not limited to, ethanol, glycerin, propylene glycol, polyethylene glycol.

Preferred buffer systems include, but are not limited to, potassium acetate, boric, carbonic, phosphoric, succinic, malic, tartaric, citric, acetic, benzoic, lactic, glyceric, gluconic, glutaric and glutamic. Particularly preferred are phosphoric, tartaric, citric, and potassium acetate.

Preferred surfactants include, but are not limited to, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene monoalkyl ethers, sucrose monoesters and lanolin esters and ethers.

Preferred preservatives include, but are not limited to, phenol, alkyl esters of parahydroxybenzoic acid, o-phenyl phenol benzoic acid and the salts thereof, boric acid and the salts thereof, sorbic acid and the salts thereof, chlorbutanol, benzyl

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alcohol, thimerosal, phenylmercuric acetate and nitrate, nitromersol, benzalkonium chloride, cetylpyridinium chloride, methyl paraben, and propyl paraben. Particularly preferred are the salts of benzoic acid, cetylpyridinium chloride, methyl paraben and propyl paraben.

Preferred sweeteners include, but are not limited to, sucrose, glucose, saccharin, and aspartame. Particularly preferred are sucrose and saccharin.

Preferred viscosity agents include, but are not limited to, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl-methylcellulose, carbomer, povidone, acacia, guar gum, xanthan gum and tragacanth. Particularly preferred are methylcellulose, carbomer, xanthan gum, guar gum, povidone and sodium carboxymethylcellulose.

Preferred fillers include, but are not limited to, lactose and microcrystalline cellulose.

Preferred plasticizers include, but are not limited to, polyethylene glycol, propylene glycol, dibutyl phthalate, and castor oil.

Preferred polymers include, but are not limited to, ethylcellulose and Eudragit S<sup>®</sup> 100 and Eudragit L<sup>®</sup> 100, both manufactured by Rohm Pharma GmbH, Weiderstadt, West Germany.

Preferred lubricants include, but are not limited to, magnesium stearate, stearic acid, and talc.

#### 1. Oral Administration of 5-ASA Pharmaceutical Compositions

The 5-ASA active ingredient can be reliably topically delivered, specifically to the entire intestinal tract, or any part thereof, preferably the large intestine, thereby substantially alleviating the symptoms of IBS-D. As stated hereinabove, an oral dosage form is preferred. The most preferred oral dosage form is one which effects topical delivery to the large intestine and is prepared by coating a solid oral dosage form with a partly methyl esterified methacrylic acid polymer, utilizing the method described in U.K. Patent Application GB 2,123,695 of Rhodes et al., published February 8,

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1984, assigned to J.B. Tillott, Ltd. hereby incorporated by reference herein.

While the coating method described therein is preferred, any coating which is insoluble at a pH below 7.0 (i.e., that generally found in the stomach and the small intestine) but soluble at pH 7.0 or above (i.e., that present in the large intestine) can be used in the practice of the present invention. Accordingly, when it is desired to effect the topical delivery of the 5-ASA active ingredient to the large intestine, any coating which is wholly- or partially-insoluble at a pH below 7.0 and soluble at pH 7.0 or above is suitable.

The partly methyl esterified methacrylic acid polymer which is preferred for use as the coating must be applied to said solid oral dosage form in a sufficient thickness so that the entire coating does not dissolve in gastrointestinal fluids at a pH below 7.0, but does dissolve at a pH of 7.0 or above. The dissolution or disintegration of the excipient coating generally does not occur until the entry of the coated dosage form into the large intestine. In particular, there is substantially no release of the 5-ASA active ingredient upstream of the colon. Further, the most preferred system for use herein when topical delivery of the 5-ASA active ingredient to the large intestine is desired involves the coating of the solid oral dosage form itself and not the coating of individual particles or granules contained therein; hence, the preferred coated dosage form is relatively inexpensive and easy to manufacture. It must be remembered, however, that any method of coating said active ingredient composition which effects the topical delivery of the active ingredient to a desired portion of the intestinal tract is suitable for use in the method of treatment described herein; therefore, an alternative and suitable method is that described in U.S. Patent 4,496,553 to Halskov, previously incorporated by reference herein.

It is expected that any anionic polymer exhibiting the requisite pH-dependent solubility profile can be used in the practice of the present invention to achieve topical delivery of

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the 5-ASA active ingredient to the large intestine. The coating chosen must be compatible with the particular 5-ASA active ingredient selected. The preferred polymers for use in the present invention are anionic carboxylic polymers. It is particularly preferred that the polymers are acrylic polymers, most preferably partly methyl-esterified methacrylic acid polymers, in which the ratio of anionic free carboxyl groups to ester groups is about 1 to 2.

A particularly suitable methacrylic acid copolymer is Eudragit S<sup>®</sup>, manufactured by Rohm Pharma GmbH, Weiterstadt, West Germany. In Eudragit S<sup>®</sup>, the ratio of free carboxyl groups to ester groups is approximately 1:2. Further, said copolymer is known to be insoluble in gastrointestinal fluids having a pH below 5.5, generally 1.5-5.5, i.e., that generally present in gastric fluid, and poorly soluble at pH above 5.5 and below 7.0, i.e., that generally present in the fluid of the small intestine. Said copolymer is soluble at pH 7.0 and above, i.e., that generally present in the colon.

Another methacrylic acid copolymer which is suitable for use in coating oral dosage forms which can be employed in the method of treatment described herein, either alone or in combination with other coatings, is Eudragit L<sup>®</sup>, manufactured by Rohm Pharma GmbH, Weiterstadt, West Germany. Eudragit L<sup>®</sup> differs from Eudragit S<sup>®</sup> only insofar as the ratio of free carboxyl groups to ester groups is approximately 1:1. Eudragit L<sup>®</sup> is also, like Eudragit S<sup>®</sup>, insoluble at pH below 5.5, generally 1.5-5.5, such as that present in gastric juice, but, unlike Eudragit S<sup>®</sup>, is readily soluble in gastrointestinal fluids having a pH of 5.5 and above, such as that present in small intestinal juice.

Eudragit L<sup>®</sup> can be used alone as a coating which would provide topical delivery of the 5-ASA active ingredient beginning at the small intestine (more proximal than the terminal ileum) via a delayed-release mechanism. In addition, Eudragit L<sup>®</sup>, being readily soluble in intestinal juice below pH 7.0, could be used in combination with Eudragit S<sup>®</sup>, soluble in intestinal juice above pH 7.0, in order to effect a delayed-release composition



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which could be formulated to topically deliver the active ingredient at various segments of the intestinal tract; the more Eudragit L<sup>®</sup> used, the more proximal release and delivery begins and the more Eudragit S<sup>®</sup> used, the more distal release and delivery begins. For an Example showing the use of Eudragit L<sup>®</sup> alone as a coating material, see Example VIII.

The coating can, and usually will, contain a plasticiser and possibly other coating excipients such as coloring agents, talc, and/or magnesium stearate, many of which are well known in the coating art. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticiser, especially dibutyl phthalate. Conventional coating techniques such as spray or pan coating are employed to apply the coating. As previously mentioned, the coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached. For the preferred coating method described herein utilizing methylacrylate copolymers when the desired site of topical delivery is the large intestine, it has been found that a coating thickness of between 40 and 150 microns usually is required. Preferably, the coating thickness is between 60 and 130 microns, and most preferably between 70 and 100 microns. For Examples of a method suitable for use in coating a solid oral dosage form of a 5-ASA active ingredient which will effect the topical delivery of said active ingredient to the large intestine, see Examples I-IV hereinbelow.

Another delayed-release type of oral dosage form suitable for achieving topical delivery of the 5-ASA active ingredient to the large intestine involves the use of a material, most preferably a resin, the dissolution of which is time-dependent, as opposed to the previously-mentioned methacrylic acid copolymer-type coatings which are pH-dependent. The topical delivery of said active ingredient to the large intestine is accomplished by embedding individual particles of said active ingredient in a slowly-disintegrating or slowly-dissolving resin which has a particular dissolution profile such that the active

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ingredient remains substantially protected by the material while the particles travel through the stomach and the small intestine of an individual and that the active ingredient is substantially completely exposed at the time the particles reach the large intestine. In particular, the preferred resin for use when employing this type of excipient material is a high-viscosity grade modified vinyl acetate resin such as Gelva C3-V30<sup>®</sup>, manufactured by The Monsanto Co., St. Louis, Missouri. Other suitable resins are carboxylated polyvinyl acetates, polyvinyl/maleic anhydride copolymers, ethylcellulose, cellulose polymers, methylacrylic acid/methyl methacrylate copolymers, waxes, and mixtures thereof, including mixtures with shellac.

While the method of treatment preferably embodies the use of a coated delayed-release tablet containing 5-ASA, other methods used to insure the topical delivery of the active ingredient to the intestinal tract can certainly be used in the treatment of IBS-D. For instance, U.S. Patent 4,496,553 to Halskov, previously incorporated by reference herein, describes a method which involves formulating 5-ASA in a sustained-release tablet and specifies ethylcellulose as the preferred coating material. Instead of utilizing the preferred method of coating tablets of 5-ASA active ingredients as the solid oral dosage form, it is granules of the 5-ASA active ingredient which are coated in the method described by Halskov. For examples of how this method can be used to prepare a composition containing the 5-ASA active ingredient suitable for use in the treatment of IBS-D which will effect the topical delivery of 5-ASA to the intestinal tract beginning with the small intestine, see Examples V-VII set forth hereinafter.

Another sustained-release oral dosage form suitable for use in the topical delivery of the 5-ASA active ingredient to the intestinal tract is described in U.S. Patent 4,780,318 to Appelgren et al., issued October 25, 1988, and assigned to Lejus Medical Aktiebolag, Molndal, Sweden, hereby incorporated by reference herein. Said oral dosage form is characterized by a core comprising the 5-ASA active ingredient, preferably in the

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form of a weak base or a weak acid, upon which core there is provided a first, inner layer of a diffusion membrane comprised of ethylcellulose and/or copolymers of polyethyl acrylate, methyl methacrylate, trimethylammonium ethyl methacrylate chloride, or mixtures thereof. Further, on said inner layer there is provided a second layer of an excipient material, preferably of anionic polymers, fatty acids, or mixtures thereof, having a  $pK_a$  of about 4.5 to about 7.0, preferably about 6.0 to about 6.5. When this outer layer has been removed by dissolution upon passage of the composition into the small intestine with the higher pH, a slow but controlled release of the 5-ASA active ingredient from the core by diffusion through the diffusion membrane occurs due to the difference in concentration on each side of said membrane. For an example of this particular pH-independent sustained-release oral dosage form, see Example XII herein.

Various other oral dosage forms are suitable for use herein for achieving the topical delivery of 5-ASA active ingredient to the intestinal tract and are described in the following U.S. Patents, all incorporated by reference herein: 4,880,794 to Halskov, issued November 14, 1989; and 4,705,515, issued November 10, 1987, 4,693,895, issued September 15, 1987, and 4,627,851, issued December 9, 1986, all of Wong et al., and all assigned to ALZA Corporation.

## 2. Rectal Administration of 5-ASA Pharmaceutical Compositions

Although it is preferable to achieve topical delivery of the 5-ASA active ingredient to the intestinal tract via an oral dosage form, rectal administration is another method of topical delivery suitable for use in the method of the present invention for the treatment of IBS-D. Rectal administration may be in the form of suppositories or enemas, or can be effected by the delivery of the 5-ASA ingredient to the large intestine via the application of a suspension, solution, emulsion, creme or the like through a tube inserted into the rectum.

One method of achieving the topical delivery of the 5-ASA active ingredient via rectal administration is an enema form comprised of a bisulfite suspension containing a 5-ASA active

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ingredient. One preferred enema suspension is that described in U.S. Patent 4,657,900 to Powell et al., issued April 14, 1987, and assigned to Rowell Laboratories, Baudette, Minnesota, hereby incorporated by reference herein. The aqueous suspension of the 5-ASA active ingredient is preferably rendered storage stable against color formation by storing the suspension in a single-dose polyethylene bottle, which is specifically adapted for the rectal administration of the suspension. The said suspension is stored in a substantially oxygen-free atmosphere and contains up to about 0.25% by weight of bisulfite. The suspension is protected from exposure to atmospheric oxygen during storage by sealing the plastic bottle, in a substantially oxygen-free atmosphere, in a plastic pouch having a low oxygen transmission rate.

If the starting 5-ASA active ingredient contains trace amounts of heavy metals, color formation as a result of their presence can be avoided by employing the bisulfite in combination with a chelating agent such as ethylenediaminetetraacetic acid (hereinafter referred to as "EDTA"). The bisulfite and the EDTA can be supplied in any convenient form, e.g., as a soluble salt thereof, such as an alkali metal salt, and can be dissolved in the water used to form the 5-ASA active ingredient solutions prior to, preferably concurrently with, or less desirably after, dissolving the 5-ASA active ingredient therein.

The 5-ASA active ingredient suspension suitable for use as an enema in the method of treatment described herein should preferably also contain a conventional bacteriostatic agent, for example sodium benzoate, to ensure against bacterial contamination. Other desired pharmaceutically-acceptable excipients and non-5-ASA active agents as described herein may also be utilized. For examples describing preferable enema suspensions, see Examples XIV-XVI.

In addition to rectal administration via the application of an enema suspension, the use of a suppository containing the 5-ASA active ingredient is suitable as a method to effect the topical delivery of 5-ASA active ingredient to the large

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intestine, thereby serving as a method of treatment for IBS-D. One type of suppository suitable for use in the present invention is described in U.S. Patent 3,932,613 to Chapura, issued January 13, 1976, assigned to Norwich Eaton Pharmaceuticals, Inc., hereby incorporated by reference herein. For an example of a suitable suppository formulation for use herein as a treatment for IBS-D, see Example XIV.

The following non-limiting Examples are provided to further illustrate the methods and compositions of the present invention.

10

Example I

Eight 5-ASA tablets, prepared as described below, are given to a patient suffering from IBS-D, 2 immediately preceding each meal and at bedtime.

A coating composition is prepared in the form of a lacquer containing the following excipients, per tablet:

<u>Excipients</u>		
20	Eudragit S100®	17.7 mg
	(manufactured by Rohm Pharma GmbH, Weiterstadt, West Germany)	
	Dibutyl phthalate	3.5 mg
	Talc	4.7 mg
	Red Iron Oxide	2.3 mg
25	Yellow Iron Oxide	0.4 mg
	Acetone	35.1 mg
	Isopropyl alcohol	157.2 mg

A coating of 5.6w/w% dried lacquer substance (i.e., about 70 microns thick) is applied by spraying the above composition onto 400mg 5-ASA caplet-shaped tablets, each weighing 507.6mg and each containing:

35

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Active ingredient

5-ASA 400.00 mg

Excipients

Lactose 76.40 mg

5 Polyvinylpyrrolidone, K29-32 8.70 mg

Magnesium stearate 1.55 mg

Talc 2.60 mg

Sodium starch glycolate 18.30 mg

10 After eight weeks of therapy, the patient does not experience abdominal pain and experiences normal and regular bowel movements.

Example II

15 A patient suffering from IBS-D is given eight 5-ASA tablets utilizing the same dosing regimen as described in Example I. The 5-ASA tablets are prepared as described in Example I, except that the active ingredients of the caplet-shaped tablet are, instead of 400mg of 5-ASA, 300mg of 5-ASA and 100mg of indomethacin.

Example III

20 A patient suffering from IBS-D is given eight 5-ASA tablets utilizing the same dosing regimen as described in Example I. The 5-ASA tablets are prepared as described in Example I, except that the active ingredients of the caplet-shaped tablet are, instead of 400mg 5-ASA, 200mg naproxen and 200mg 5-ASA.

25 Example IV

A patient suffering from IBS-D is given eight 5-ASA tablets utilizing the same dosing regimen as described in Example I. The 5-ASA tablets are prepared as described in Example I, except the active ingredients of the caplet-shaped tablet are, instead of 30 400mg 5-ASA, 300mg tebufelone and 100mg 5-ASA.

Example V

A patient suffering from IBS-D is given eight 5-ASA tablets, 2 immediately preceding each meal and at bedtime, except the 5-ASA tablets are prepared so that they achieve topical delivery 35 of 5-ASA to both the small intestine and the large intestine. After 3-6 weeks of therapy, the patient is free of abdominal pain

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and is experiencing regular and normal bowel movements. The tablets are prepared as described below:

A. Preparation of 5-ASA granules

5        250g of 5-ASA are granulated to a particle size of from 0.7-1mm with 25g of polyvinylpyrrolidone dissolved in isopropanol (1:9W/W). Upon evaporation of the isopropanol, the resulting dry granulate is sprayed with 45g of ethylcellulose dissolved in acetone (3:97W/W) resulting in granulate particles individually  
10       coated with ethylcellulose upon evaporation of the acetone.

B. Preparation of filler granules

      270g of microcrystalline cellulose and 60g of potato starch are granulated with about 33g of the above polyvinylpyrrolidone  
15       solution to the same particle size.

C. Preparation of the 5-ASA tablet

      The resulting 320g of the 5-ASA coated granules prepared in Part A. hereinabove is mixed with a lubricant mixture consisting  
20       of 3g zinc stearate and 27g talc and with the filler granulate prepared in Part B. hereinabove to form 650g of total granulate. Said total granulate is pressed to form tablets with a diameter of 13.5mm and a weight of 650 mg/tablet, each containing 250mg of 5-ASA.

25

Example VI

      A patient suffering from IBS-D is given eight tablets at intervals described in Example V. The tablets are prepared according to the method set forth in Example V herein except that acetone is used instead of isopropanol in the polyvinylpyrrolidone solution in Parts A. and B.  
30

Example VII

      A patient suffering from IBS-D is given eight tablets at intervals described in Example V. The tablets are prepared according to the method set forth in Example V, except that the  
35       ethylcellulose in Part A. is replaced with hydroxypropylmethylcellulose.

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Example VIII

A patient suffering from IBS-D is given four 5-ASA tablets prepared as described below, one immediately preceding each meal and at bedtime. The tablets are prepared so that they achieve the topical delivery of 5-ASA to the small intestine is described below.

A coating composition is prepared from a lacquer containing the following excipients, per tablet:

10	Eudragit L100®	40.0 mg
	(manufactured by Rohm Pharma GmbH, Weiterstadt, West Germany)	
	Isopropyl alcohol	210.0 mg
15	Dibutyl phthalate	3.1 mg
	Castor oil	3.1 mg
	Acetone	143.8 mg

A coating weight of 5.0w/w% dried lacquer substance (about 75 microns thick) is applied by conventional pan coating to 600mg 5-ASA tablets, so that oval-shaped tablets, each weighing 800mg, result. The composition of each tablet is as follows:

	<u>Active ingredient</u>	
25	5-ASA	600 mg
	<u>Excipients</u>	
	Hydroxypropylmethylcellulose	10 mg
	Microcrystalline cellulose	150 mg
	Alginic acid	10 mg
30	Stearic acid	30 mg

After 6 weeks of therapy, the patient is free of abdominal pain and experiences normal and regular bowel movements.

Example IX

A patient suffering from IBS-D is given 5-ASA tablets at intervals described in Example VIII. The tablets are prepared as



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described in Example VIII, except that the active ingredients of the caplet-shaped tablet are, instead of 600mg 5-ASA, 400mg 5-ASA and 200mg indomethacin.

Example X

5 A patient suffering from IBS-D is given 5-ASA tablets at intervals described in Example VIII. The tablets are prepared as described in Example VIII, except that the active ingredients of the caplet-shaped tablet are, instead of 600mg 5-ASA, 300mg naproxen and 300mg 5-ASA.

10

Example XI

A patient suffering from IBS-D is given 5-ASA tablets at intervals described in Example VIII. The tablets are prepared as described in Example VIII, except that the active ingredients of the caplet-shaped tablet are, instead of 600mg 5-ASA, 400mg  
15 tebufelone and 200mg 5-ASA.

Example XII

A patient suffering from IBS-D is given 12 of the 250mg 5-ASA tablets, 3 immediately before each meal and at bedtime. 5-ASA tablets prepared as described below are suitable for  
20 effecting the topical delivery of 5-ASA to the intestinal tract.

Granulated 5-ASA active ingredient having a granular size of 0.6mm to 1.5mm and comprising 60% of active ingredient are provided with a diffusion membrane as follows:

5-ASA active ingredient granules are sprayed with a solution  
25 of 50% by weight of ethylcellulose and 50% by weight of polyethyl acrylate-methyl methacrylate:trimethylammonium ethyl methacrylate:trimethylammonium ethyl methacrylate chloride copolymer with the weight % 65:32.5:2.5 (Eudragit RL®, manufactured by Rohm Pharma GmbH, Weiderstadt, West Germany)  
30 dissolved in methylene chloride/isopropanol in a fluidized bed. The concentration of polymer in the solvent mixture is 4% by weight.

The 5-ASA granules (equivalent to 250mg 5-ASA active ingredient) covered with a diffusion membrane are covered with an  
35 outer layer of hydroxypropylcellulose phthalate dissolved in

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methylene chloride/ethanol mixture, utilizing the same technique described above for the diffusion membrane.

The inner diffusion membrane is applied in an amount of 12g/m<sup>2</sup> and the outer layer of anionic polymer is applied in an amount of 16g/m<sup>2</sup>.

After 3-6 weeks of therapy, the patient's abdominal pain diminishes and regular and normal bowel movements resume.

#### Examples XIII

A patient suffering from IBS-D is administered a suppository prepared as described below, twice daily, for a period of 3-6 weeks. The suppository containing 5-ASA is prepared containing the following ingredients:

	<u>Active ingredient</u>	
15	5-ASA	0.50 g
	<u>Excipients</u>	
	Theobroma oil	0.95 g
	White wax	0.15 g

The suppository is prepared utilizing the following method:

The theobroma oil and the white wax are melted in a suitable vessel with gentle heat (approximately 40°-60°C) to form a melted excipient base. The 5-ASA is combined with said base until uniformly dispersed. The melted base containing the 5-ASA is poured into a chilled mold that is lightly lubricated with mineral oil. The mold is then subjected to cold temperatures (ideally, below freezing) until the melted base solidifies. The formed suppository is then removed from the mold and is then wrapped in aluminum foil.

For maximum benefit, the patient should retain each suppository in the rectum for 1-3 hours, or longer, if possible. At the conclusion of that therapy, the patient has no abdominal pain and is experiencing normal and regular bowel movements.

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Example XIV

A patient suffering from IBS-D is administered the enema prepared as described above, once daily for 3-6 weeks, at bedtime.

- 5 The enema is prepared as a 5-ASA suspension having the following composition:

	<u>Active ingredient</u>	<u>% W/W</u>	<u>Per 10,000 liters</u>
	5-ASA	10.2	2,550.0 g
	<u>Excipients</u>		
10	Potassium metabisulfite	0.12	29.50 g
	Carbopol® 934 P	0.08	18.75 g
	(manufactured by The B.F. Goodrich Co., Cleveland, Ohio)		
15	Edetate disodium	0.10	25.0 g
	Potassium acetate	0.43	102.50 g
	Xanthan gum	0.25	62.5 g
	(manufactured by Merck, Sharpe & Dolhm, Chicago, Illinois)		
20	Sodium benzoate	0.10	25.0 g
	Purified water	24.00	6,000.0 g
	Purified water to bring to volume of	64.72	25,000.0 g
25			

The 5-ASA suspension is prepared as described below:

A. Purification of 5-ASA

- 100g of 95% 5-ASA (technical grade) is dissolved in 2,000ml of 2N HCl (AR grade) while heating to 60°C-80°C to facilitate rate of solution. The hot solution is filtered through a suitable acid stable filtering medium (analytical filter paper) to remove any undissolved material. 20g of decolorizing activated charcoal (e.g. Darco G-60) is added to the tan colored hot filtrate and mixed for approximately 5 minutes while the temperature of the solution is maintained at about 60°C. The solution is once again filtered through the filtering medium as

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described above and the filtrate is cooled to 15°C-20°C. The pH of the filtrate is raised to about 3.5-4.0 with approximately 560ml of high purity 28.6% (7.14N) NaOH. At a pH of about 1.8-2.0, the 5-ASA begins to precipitate. When precipitation is completed, the precipitated 5-ASA is collected by vacuum filtration. The mother liquor is retained and washed with U.S.P. water until the rinse is free of sodium and chloride. The mother liquor is then washed twice each time with 200ml of anhydrous ethanol (SDA-JA). The washed 5-ASA is then dried in a vacuum oven.

B. Preparation of a Stable Aqueous 5-ASA Suspension

2,000g water (RODI) is charged into a 10-gallon stainless steel tank and 25.0g sodium benzoate is dissolved therein using a Lightning Mixer. 18.75g Carbopol® 934 P (manufactured by B.F. Goodrich Co., Cleveland, OH) is added slowly while mixing until a lump-free dispersion of Carbopol® is produced. The resulting solution is mixed for one hour and is allowed to set overnight at room temperature with the tank covered lightly. The dispersion is milled for 10 minutes using 1 hp G&W mill and is then set for 30 minutes to deaerate. 25.00g disodium EDTA, 29.5g of potassium metabisulfite and 102.5g of potassium acetate is added to the solution while the solution is stirred with a Lightning Mixer. 62.5g xanthan gum is slowly added to the mixture until it dissolves. 4,000g water is charged into a 5-gallon stainless steel container and 2,550.0g of 5-ASA purified according to Part A. above is added to the water in the stainless steel container. A slurry is made from the water and the 5-ASA using a Lightning Mixer. The resulting slurry is added to the previously prepared dispersion and mixed for 15 minutes. The resulting mixture is brought to 25,000g with water (RODI) and mixed for one hour. The resulting product is strained through a 40-mesh in-line strainer during the filling operation which is described below.

C. Preparation of packaged 5-ASA Enema

The suspension prepared in part B. above is poured into a commercially available 60ml capacity single-dose collapsible white opaque low-density polyethylene bottles with snapping

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necks. Nitrogen gas is flushed into the bottles to displace head space air and each is capped with a special snap-on lubricated rectal applicator covered with a press fitted removable protective plastic cap.

- 5       An oxygen barrier is provided in the bottles filled as described above by inserting each of the bottles into a polyester/aluminum foil/polyethylene laminate heat sealable 6-1/2" x 8" plastic pouch (Kapak Corporation, St. Louis Park, MN) and flushing each pouch with nitrogen and immediately heat  
10       sealing each pouch.

A patient suffering from IBS-D is administered the enema prepared as described above once daily for 3-6 weeks and at the conclusion of such therapy, is free of abdominal pain and is experiencing normal and regular bowel movements.

15                               Example XV

An enema suspension suitable for use in the treatment of IBS-D is prepared as described in Example XIV, except that Step A., the purification of the 5-ASA, is conducted as described below:

- 20       1810g of USP water is charged into a 4 liter beaker and 196g sulfuric acid (RR) is slowly added to the water while stirring. 100g (pure beads) of technical grade (about 90-95% purity) 5-ASA is slowly added and dissolved. The temperature of the resulting solution is maintained at 60°C-80°C. 20g activated charcoal is  
25       added to the solution and the solution is stirred for 5-30 minutes. The temperature is maintained at 60°C-80°C while the charcoal suspension is filtered through analytical filter paper. The filtrate is cooled to 0°C-5°C. 0.5g sodium bisulfite USP is added to the suspension. 160g sodium hydroxide USP is dissolved  
30       in 400g water USP and the solution is cooled to 0.5°C. The cooled solution is next slowly added to the 5-ASA solution while stirring to about pH 3.5, using a pH meter. Additional 1N sodium hydroxide may be utilized to properly adjust the pH if needed. The resultant 5-ASA slurry is cooled to 0°C-5°C and the 5-ASA  
35       crystals are separated from the slurry using a Büchner funnel and vacuum pump. The filtrate is discarded and the crystal bed is

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rinsed with USP water at 2°C-5°C until the rinse is free of sulfate and sodium ions. A vacuum is used to remove water from the crystal bed. The crystal bed is rinsed with 300g alcohol SOA-3A. A vacuum is used to remove alcohol from the crystals.

5 After the crystals are trayed out, they are dried at 75°C-90°C for 6-8 hours.

#### Example XVI

An enema suspension suitable for use in the treatment of IBS-D is prepared as described in Example XIV above, except that

10 the stable aqueous 5-ASA suspension is made utilizing the same procedure and the same excipients as set forth in Part B. therein, except that the amounts of the excipients used are as set forth below:

15	Water (RODI)	18,750.00 g
	Sodium benzoate	20.00 g
	Carbopol®.934 P	25.00 g
	Disodium EDTA	22.50 g
	Potassium metabisulfite	70.00 g
20	Potassium acetate	65.00 g
	Xanthan gum	80.00 g
	5-ASA	1,500.00 g
	Water (RODI)	3,200.00 g

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#### Example XVII

A 63-year-old Caucasian male presents with moderate to severe abdominal pain and frequent and severe diarrhea. The patient is diagnosed as having IBS-D by the exclusion of organic pathology. The patient is treated with a total daily drug dose

30 of 4.8g 5-ASA via the ingestion of 12 tablets, 3 immediately preceding each meal and at bedtime, prepared as described in Example I.

After 8 weeks of the above-described therapy, the patient's pain is substantially alleviated and he experiences normal and

35 regular bowel movements.

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Example XVIII

5 A 57-year-old Caucasian female presents with frequent diarrhea and generally moderate abdominal pain which intensifies shortly before she experiences the diarrhea. The patient is diagnosed as having IBS-D by the exclusion of organic pathology. The patient is treated with a total daily dose of 3.2g of 5-ASA via the ingestion of 8 tablets, 2 immediately preceding each meal and at bedtime, prepared as described in Example I.

10 After 6 weeks of the above-described therapy, the patient is experiencing normal and regular bowel movements and her abdominal pain subsides.

Example XIX

15 A 34-year-old Caucasian male presents with alternating moderate diarrhea and mild constipation and constant mild abdominal pain. The patient is diagnosed as having IBS-D by the exclusion of organic pathology. The patient is treated with a total daily dose of 2.4 grams of 5-ASA via the ingestion of 6 tablets, 2 immediately preceding each meal, prepared as described in Example I.

20 After 4 weeks of the above-described therapy, the patient has substantially no abdominal pain and has normal and regular bowel movements.

Example XX

25 A 50-year-old Caucasian female presents with frequent diarrhea accompanied by moderate to severe abdominal cramping. The patient is diagnosed as having IBS-D by the exclusion of organic pathology. The patient is treated with 2.4 grams of 5-ASA via the ingestion of 6 tablets, 2 immediately before each meal, prepared as described in Example I.

30 After 4 weeks of the above-described therapy, the patient has substantially no abdominal cramping and is experiencing normal and regular bowel movements.

Example XXI

35 A 68-year-old Caucasian male presents with painless but frequent diarrhea. The patient is diagnosed as having IBS-D by

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the exclusion of organic pathology. The patient is treated with a total daily dose of 1.6g of 5-ASA via the ingestion of 4 tablets, one immediately preceding each meal and at bedtime, prepared as described in Example I.

5       After 2 weeks of the above-specified therapy, the patient is experiencing normal and regular bowel movements.

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## WHAT IS CLAIMED IS:

1. A novel method of treatment for a human or other mammal afflicted with IBS-D which comprises the topical delivery to the intestinal tract of said human or other mammal of a safe and effective amount of a pharmaceutical composition consisting essentially of a 5-ASA active ingredient and pharmaceutically-acceptable excipients.
2. A method of treatment according to Claim 1 wherein said topical delivery is accomplished by the oral administration of said pharmaceutical composition.
3. A method of treatment according to Claim 2 wherein the active ingredient is topically delivered to the large intestine.
4. A method of treatment according to Claim 3 wherein the pharmaceutical composition is a delayed-release composition.
5. A method of treatment according to Claim 4 wherein said composition consists essentially of the active ingredient coated with a pH-dependent coating material, which is insoluble at a pH of below 7.0 and soluble at a pH of 7.0 and above.
6. A method of treatment according to Claim 5 wherein the coating material is an anionic carboxylic polymer.
7. A method of treatment according to Claim 6 wherein the anionic carboxylic polymer is an acrylic polymer.
8. A method of treatment according to Claim 7 wherein the acrylic polymer is a methyl-esterified methacrylic acid polymer.
9. A method of treatment according to Claim 8 wherein the ratio of anionic free carboxylic groups to ester groups in the methyl-esterified methacrylic acid polymer is about 1 to 2.

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10. A method of treatment according to Claim 9 wherein the coating thickness is from about 40 microns to about 150 microns.

11. A method of treatment according to Claim 10 wherein the coating thickness is from about 60 microns to about 130 microns.

12. A method of treatment according to Claim 11 wherein the coating thickness is from about 70 microns to about 100 microns.

13. A method of treatment according to Claim 4 wherein said composition consists essentially of the active ingredient in combination with a time-dependent excipient material which has a particular dissolution profile such that said active ingredient remains substantially protected by the said material while said active ingredient travels through the stomach and the small intestine of said human or other mammal and that said active ingredient is substantially completely exposed at the time the active ingredient reaches the large intestine.

14. A method of treatment according to Claim 13 wherein said excipient material is a resin selected from the group consisting of, but not limited to, vinyl acetates, carboxylated polyvinyl acetates, polyvinyl maleic anhydride copolymers, ethylcellulose, cellulose polymers, methylacrylic acid/methyl methacrylate copolymers, waxes, and mixtures thereof.

15. A method of treatment according to Claim 2 wherein the active ingredient is topically delivered to the small intestine.

16. A method of treatment according to Claim 15 wherein the pharmaceutical composition is a delayed-release pharmaceutical composition.

17. A method of treatment according to Claim 15 wherein said composition consists essentially of the active ingredient

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coated with a pH-dependent coating material, which is insoluble at a pH of below 5.5 and soluble at a pH of 5.5 and above.

18. A method of treatment according to Claim 17 wherein the coating material is a methyl-esterified methacrylic acid polymer wherein the ratio of free carboxylic groups to ester groups is about 1 to 1.

19. A method of treatment according to Claim 15 wherein the pharmaceutical composition is a sustained-release pharmaceutical composition.

20. A method of treatment according to Claim 19 wherein said composition consists essentially of granules of said active ingredient coated with pharmaceutically-acceptable excipients.

21. A method of treatment according to Claim 20 wherein said pharmaceutically-acceptable excipient is ethylcellulose.

22. A method of treatment according to Claim 1, wherein said topical delivery of the active ingredient to the large intestine is accomplished by the rectal administration of a pharmaceutical composition.

23. A method of treatment according to Claim 22 wherein said pharmaceutical composition is a suspension administered in the form of an enema.

24. A method of treatment according to Claim 23 wherein the enema suspension contains from about 0.01% to about 0.25% bisulfite by weight.

25. A method of treatment according to Claim 24 wherein the enema suspension contains from about 1.0% to about 25.0% by weight of the active ingredient.

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26. A method of treatment according to Claim 25 wherein the enema suspension additionally contains a chelating agent.

27. A method of treatment according to Claim 22 wherein said pharmaceutical composition is administered in the form of a suppository.

28. A method of treatment according to Claim 2 wherein said active ingredient is administered in a total daily dose of from about 1.0g to about 6.0g.

29. A method of treatment according to Claim 28 wherein said total daily dose is from about 2.0g to about 5.0g.

30. A method of treatment according to Claim 29 wherein said total daily dose is from about 2.4g to about 4.8g.

31. A method of treatment according to Claim 22 wherein said active ingredient is administered in a total daily dose of from about 1.0g to about 4.0g.

32. A method of treatment according to Claim 1 wherein said pharmaceutical composition additionally comprises non-5-ASA active agents.

33. The use of 5-ASA for the manufacture of a medicament for the treatment of IBS-D, said treatment characterized in that it comprises the topical delivery to the intestinal tract of said human a safe and effective amount of a pharmaceutical composition, preferably by the oral administration thereof, consisting essentially of a 5-ASA active ingredient and pharmaceutically-acceptable excipients.

34. The use of 5-ASA according to Claim 33, wherein the active ingredient is topically delivered to the large intestine.

35. The use of 5-ASA according to Claim 33, wherein the pharmaceutical composition is a delayed-release composition, preferably wherein said composition consists essentially of the active ingredient coated with a pH-dependent coating material, preferably an acrylic polymer, most preferably a methyl-esterified methacrylic acid polymer, which is insoluble at a pH of below 7.0 and soluble at a pH of 7.0 and above.

36. The use of 5-ASA according to Claim 35 wherein the coating thickness is from 40 microns to 150 microns, preferably from 60 microns to 130 microns; and most preferably from 70 microns to 100 microns.

37. The use of 5-ASA according to Claim 33, wherein said composition consists essentially of the active ingredient in combination with a time-dependent excipient material which has a particular dissolution profile such that said active ingredient remains substantially protected by the said material while said active ingredient travels through the stomach and the small intestine of said human or other mammal and that said active ingredient is substantially completely exposed at the time the active ingredient reaches the large intestine.

38. The use of 5-ASA according to Claim 33, wherein the active ingredient is topically delivered to the small intestine.

39. The use of 5-ASA according to Claim 38, wherein said composition consists essentially of the active ingredient coated with a pH-dependent coating material, which is insoluble at a pH of below 5.5 and soluble at a pH of 5.5 and above, preferably wherein said coating material is a methyl-esterified methacrylic acid polymer wherein the ratio of free carboxylic groups to ester groups is about 1 to 1.

40. The use of 5-ASA according to Claim 38, wherein the pharmaceutical composition is a sustained-release pharmaceutical composition, preferably wherein said composition consists essentially of granules of said active ingredient coated with

pharmaceutically-acceptable excipients, most preferably wherein said pharmaceutically-acceptable excipient is ethylcellulose.

41. The use of 5-ASA according to Claim 33, wherein said topical delivery of the active ingredient to the large intestine is accomplished by the rectal administration of a pharmaceutical composition, preferably in the form of a suspension administered in the form of an enema, most preferably wherein the enema suspension contains from 0.01% to 0.25% bisulfite by weight, and from 1.0% to 25.0% by weight of the active ingredient.

42. The use of 5-ASA according to Claim 33, wherein said active ingredient is administered in a total daily dose of from 1.0g to 6.0g, preferably from 2.0g to 5.0g, most preferably from 2.4g to 4.8g.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/01848

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/40,31/35,31/21

US CL :514/427,460,510

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/427,460,510

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS AND CAS ONLINE: LOVASTATIN, PRAVASTATIN, FLUVASTATIN, SIMVASTATIN, HMG-CoA VERDUCTASE INHIBITOR, ANGIOPLAS?, STENOSIS, RESTENOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,211,777 (CHAMBERS) 08 July 1980, see column 1, lines 8-19; column 2, lines 35-41; column 3, line 65-column 4, line 2.	1-42
Y	US, A, 4,657,900 (POWELL ET AL.) 14 April 1987, See entire document.	1-42
Y	US, A, 4,496,553 (HALSKOV) 29 January 1985, See entire document.	1-42
Y	GB, A, 2,123,695 (RHODES ET AL.) 01 May 1985, See entire document.	1-42

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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* P* document published prior to the international filing date but later than the priority date claimed		

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